

Case Report

Atypical carcinoid of the uterine cervix with aggressive clinical behavior: A case report



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ARTICLE INFO

Article history:

Received 15 August 2013

Accepted 15 October 2013

Available online 23 October 2013

Keywords:

Atypical carcinoid tumor

Uterine cervix

Background

Neuroendocrine tumors of the uterine cervix are rare, accounting for less than 5% of cervical cancers (Albores-Saavedra et al., 1997; Viswanathan et al., 2004). The etiology and clinicopathological features of these neuroendocrine tumors remain unknown. A PubMed search revealed only 14 previously reported cases of atypical carcinoid of the uterine cervix in the literature, and the clinical course of many of them is unknown (Boruta et al., 2001; Gilks et al., 1997; Koch et al., 1999; McCusker et al., 2003; Wang et al., 2006; Wistuba et al., 1999). A recent consensus conference suggested four general categories of neuroendocrine tumors of the uterine cervix, analogous to pulmonary neuroendocrine tumors: typical and atypical carcinoid tumors, large cell neuroendocrine carcinomas, and small cell carcinomas (Albores-Saavedra et al., 1997).

We herein report a case of International Federation of Gynecology and Obstetrics (FIGO) stage IB2 atypical carcinoid of the uterine cervix with aggressive clinical behavior.

Case

A 44-year-old Japanese woman (gravid 2, para 2) had abnormal Pap smear results. There was nothing noteworthy in her family or medical histories. There were no abnormalities of the vaginal wall or

parametrium. A subsequent colposcopy-directed punch biopsy of the cervix was performed, and neuroendocrine carcinoma of the uterine cervix was observed (suspected small cell carcinoma).

An immunohistochemical study revealed that the tumor cells were immunoreactive for synaptophysin, chromogranin A, CK7, CK20, and CK CAM5.2. They were negative for CD56, CK5/6, and CK 34βE12.

Magnetic resonance imaging revealed a focal tumor of the cervix with a contrast effect, a submucosal uterine myoma, and no obvious disease outside the uterus (Fig. 1a). In addition, fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scanning demonstrated the absence of a metastatic lesion outside the uterus and the presence of high FDG uptake within the cervix (Fig. 1b).

The patient was diagnosed with stage IB2 advanced cervical cancer according to the 2008 FIGO criteria. Routine laboratory tests and serum squamous cell antigen, carcinoembryonic antigen, carbohydrate antigen (CA)19-9, CA125, CA72-4, and neuron-specific enolase were within normal limits.

After the diagnosis was made, radical hysterectomy with systemic pelvic lymph node dissection and bilateral salpingo-oophorectomy were performed. The uterus in the modified radical hysterectomy specimen showed a 40 × 55-mm tumor localized to the uterine cervix (Fig. 2). Cytologically, the tumor mostly comprised ovoid to columnar cells of various sizes. The cells had relatively abundant cytoplasm, oval nuclear pleomorphism, and irregularity. Histology of the lesion revealed that the tumor focally extended into the stroma with palisading of columnar cells and rosette-like structures. Increased mitotic activity (1–5 mitotic figures in every 10 high-power fields) was seen within the tumors (Fig. 3a).

An immunohistochemical study was performed. Most tumor cells were strongly positive for chromogranin A and synaptophysin. 75% of the cells were positive for Ki-67/MIB-1 (Fig. 3b–d). Lymphovascular invasion was evident. No metastases were found in the 63 resected lymph nodes (pT1B2N0M0). The combination of the hematoxylin–eosin morphologic findings and immunohistochemical expression profile confirmed the diagnosis of an atypical carcinoid tumor of the uterine cervix.

Following the operation, the patient underwent adjuvant-combined chemotherapy with CPT-11 + cisplatin (CPT-11 at 60 mg/m² was administered intravenously on days 1, 8, and 15 in combination with cisplatin at 60 mg/m² on day 1) over 4 weeks and was followed-up. Four months after the chemotherapy, the patient complained of back pain, and CT demonstrated hydronephrosis of both kidneys secondary to a recurrent tumor around the ureteral orifice. In addition, PET/CT revealed hydronephrosis and a recurrent tumor around the pelvic

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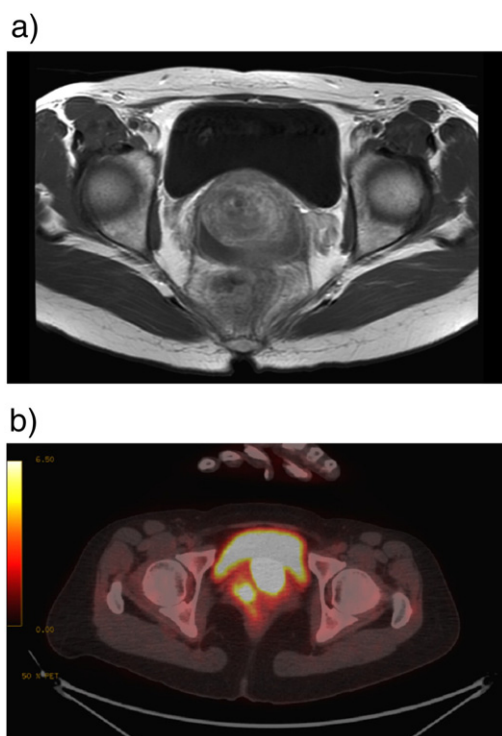


Fig. 1. (a) Preoperative pelvic magnetic resonance imaging revealed a focal tumor of the cervix with a contrast effect. (b) Fluorodeoxyglucose positron emission tomography/computed tomography scanning demonstrated high fluorodeoxyglucose uptake in the cervix.

floor of both kidneys, liver metastasis, and peritoneal dissemination. Bilateral nephrostomies were thus established. As second-line chemotherapy, the patient underwent three courses of the TC regimen (paclitaxel at 175 mg/m² + CBDCA 5AUC). She subsequently developed severe abdominal and perineal pain and ileus after three courses of the monthly TC regimen. Dietary intake became difficult. She died of the disease 13 months after the initial operation.

Discussion

A recent consensus conference suggested four general categories of neuroendocrine tumors of the uterine cervix, analogous to pulmonary neuroendocrine tumors: typical and atypical carcinoid tumors, large cell neuroendocrine carcinomas, and small cell carcinomas (Albores-Saavedra et al., 1997). Among these categories, the incidence of small

cell neuroendocrine carcinoma is the highest, accounting for about 80% of all cases; the other subtypes are rare. Human papillomavirus type 18 was found in 40% of cases of one series, whereas type 16 was found in only 28% (Albores-Saavedra et al., 1997).

Clinically, neuroendocrine carcinomas account for less than 5% of all cervical carcinomas. Neuroendocrine tumors of the cervix are characterized by a younger patient age at onset (Savorgaonkar et al., 1996), earlier distant metastasis, and a worse prognosis compared with other histological types. While most patients have a low-stage tumor at the time of diagnosis, the outlook is poor nonetheless. Walker et al. (1988) reported that 75% of patients die within 1 year.

Carcinoid tumors can occur systemically and have been reported in the lung, pancreas, gastrointestinal tract, and thyroid. Albores-Saavedra et al. (1972) was the first to report an atypical carcinoid of the uterine cervix. Since then, the etiology and clinicopathological features have remained unknown because of the rarity of these tumors. Among the carcinomas of the cervix with neuroendocrine differentiation, small cell carcinomas are well characterized (Gilks et al., 1997). Non-small cell neuroendocrine carcinomas of the uterine cervix, however, have rarely been described and are probably underdiagnosed or misdiagnosed (Albores-Saavedra et al., 1976, 1979; Park et al., 2011). Immunohistochemical studies including synaptophysin and chromogranin A are useful for detecting neuroendocrine differentiation, and strong Ki-67/MIB-1 labeling indicates the malignant characteristics of neuroendocrine tumors.

The therapy for neuroendocrine carcinoma of the uterine cervix remains controversial because of the rarity of these tumors. Although various chemotherapeutic regimens have been tried, none is associated with a good response. In recent years, novel treatment approaches to small cell carcinoma of the cervix have attempted to replicate successful treatments for small cell carcinoma of the lung. Therefore, patients with neuroendocrine carcinoma of the cervix tend to receive combination chemotherapy comprising etoposide + cisplatin (Boruta et al., 2001; Chang et al., 1998; Hoskins et al., 2003) or CPT-11 + cisplatin in accordance with the standard chemotherapy for primary small cell lung cancer (Noda et al., 2002). However, there is no evidence of treatment specific to other subtypes of neuroendocrine tumors of the cervix, including atypical carcinoids. The success of concurrent chemoradiation for other types of locally advanced cervical cancer has also influenced the management of neuroendocrine carcinoma of the cervix.

Several case reports and small case series involving patients with small cell carcinoma of the uterine cervix have indicated encouraging outcomes in patients treated with a combination of radical hysterectomy or radiation therapy and chemotherapy. However, the numbers of patients and follow-up periods have been insufficient to determine whether chemotherapy can improve the outcome of patients with small cell carcinoma of the cervix (Boruta et al., 2001; Lee et al., 2008; McCusker et al., 2003; Viswanathan et al., 2004; Wang et al., 2006).

A PubMed search revealed only 14 previously reported cases of atypical carcinoid of the uterine cervix, and the clinical course of many of them is unknown (Boruta et al., 2001; Gilks et al., 1997; Koch et al., 1999; McCusker et al., 2003; Wang et al., 2006; Wistuba et al., 1999).

In our case, because it was expected that radiation therapy is not effective in carcinoid tumors (Louka et al., 1982), the patient was treated with adjuvant chemotherapy alone. Tangjitgamol et al. (2007) reported good results with the TC regimen against large cell neuroendocrine carcinomas. Therefore, our patient was treated with this regimen after her recurrence, but the tumor progression was not suppressed. After her recurrence, she did not wish to undergo radiotherapy.

Hoskins et al. (2003) reported encouraging results using concurrent chemoradiation in patients with advanced disease. Routine inclusion of para-aortic irradiation in their protocol resulted in a 3-year survival rate of 60% and failure-free survival rate of 57%. Viswanathan (Viswanathan et al., 2004) reported that the probability of recurrence within the radiation fields is low (only 2 of 15 patients) among patients who were treated with radiation therapy. Inclusion of concurrent

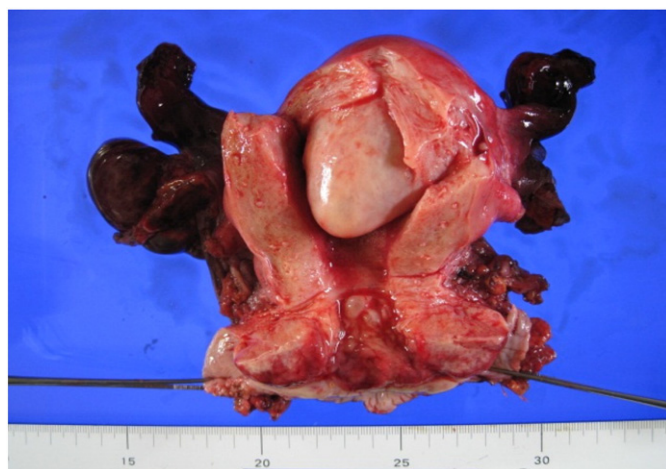
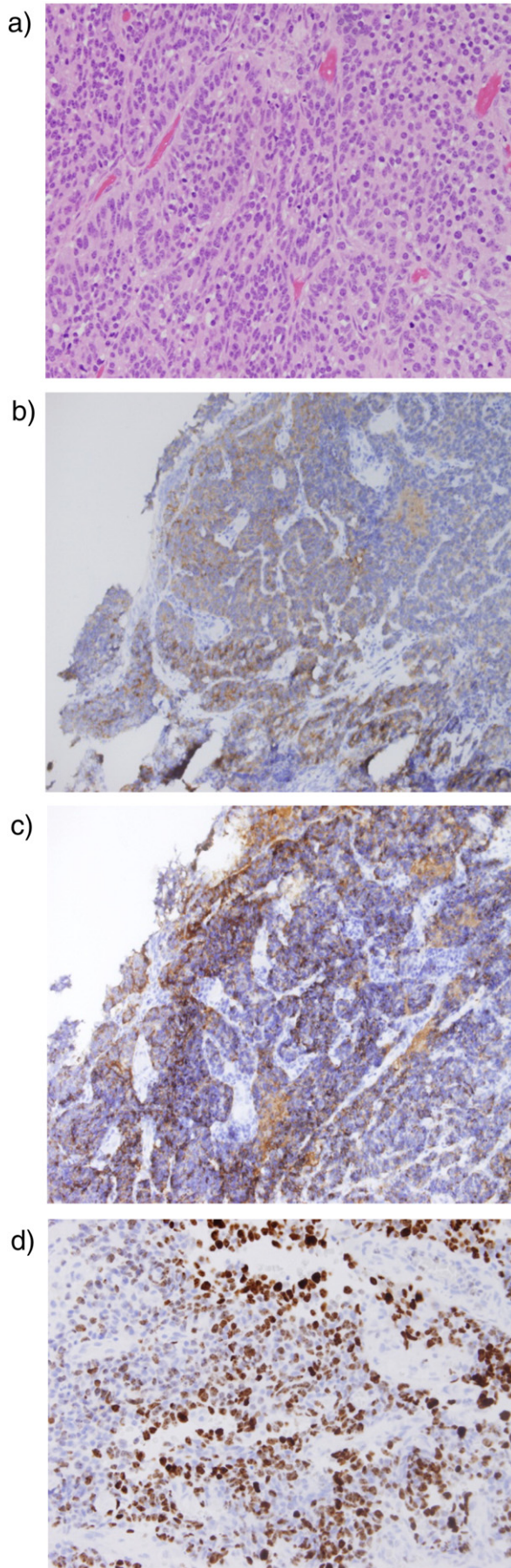


Fig. 2. Macroscopic findings of the surgical specimen.



chemoradiation after radical hysterectomy may improve the results of combined-modality treatment similar to small cell carcinoma, even atypical carcinoid.

In conclusion, we have reported a case of an atypical carcinoid of the uterine cervix with resistance to CPT-11 + cisplatin and TC chemotherapy and strong Ki-67/MIB-1 labeling. Because of the rarity of atypical carcinoid of the uterine cervix, it may be extremely difficult to establish a standard treatment by performing randomized controlled trials.

Conflict of interest

None of the authors have any conflicts of interest associated with this study.

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Fig. 3. Histological findings of atypical carcinoid. (a) The tumor focally extends into the stroma with palisading of columnar cells and rosette-like structures. The cells had relatively abundant cytoplasm, oval nuclear pleomorphism, and irregularity ($\times 400$ hematoxylin-eosin). (b) Chromogranin A on immunohistochemical study ($\times 200$). (c) Synaptophysin on immunohistochemical study ($\times 200$). (d) Ki-67/MIB-1 on immunohistochemical study ($\times 400$).